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EXAMINER
HUYNH, PHUONG N

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/713,136	Applicant(s) TUCK ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- Th MAILING DATE of this communication appears on th cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7,8 and 11-107* is/are pending in the application.

4a) Of the above claim(s) *11-42, 43-49, 52-59, 62, 64-70, 73, 76-82, 85, and 87-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7,8,50,51,60,61,63,71,72,74,75,83,84,86 and 90-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

DETAILED ACTION

1. Claims 1-3, 7-8, and 11-107 are pending.

2. The following new grounds of rejection are necessitated by the amendment filed 5/6/02 and 9/30/02.

3. The request for rejoinder of the process claims upon allowance of the product claims under consideration filed 5/6/02 is acknowledged.

4. Claims 11-42, 43-49, 52-59, 62, 64-70, 73, 76-82, 85, and 87-89 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected inventions.

5. Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 83-84, 86, and 90-107 that read on species "Amb a1" as the specific antigen and "AACGTTCG" as a specific ISS are being acted upon in this Office Action.

6. The drawings, filed 11/14/00, stand not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review mailed 11/5/01. Appropriate action is required.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 83-84, 86, and 90-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a population of conjugate molecules said molecules comprising a ragweed pollen allergen such as Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence *consisting* of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population is such that the ratio of (i) concentration of ISS-antigen conjugate to (ii) concentration of antigen required for 50% inhibition of antigen-specific antibody to antigen is about 3.5 to about 6.0; (2) A population of conjugate molecules said

molecules comprising a ragweed pollen allergen such as Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence *consisting* of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides a 40% histamine release from basophils of an allergen-sensitized individual is greater than about 500, said ratio is calculated as the ratio of (i) concentration of ISS-allergen conjugate to (ii) concentration of antigen required for 40% histamine release from basophils from an allergen sensitized individual; (3) A population of conjugate molecules, said conjugate molecules comprising a ragweed pollen allergen such as Amb a1 and a polynucleotide *consisting* of an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence consisting of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule; (4) A composition comprising the population of conjugate molecules, said conjugate molecules comprising a ragweed pollen allergen and a polynucleotide *consisting* of an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence *consisting* of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule in a pharmaceutically acceptable excipient; (5) A population of conjugate molecules said molecules comprising a ragweed pollen allergen such as Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence consisting of the sequence such as the ones recited in claims 79, 81, 82, 84 and 85, and wherein the extent of conjugation in the population provides an average of ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least 1.1; (6) A composition comprising the population of conjugate molecules said molecules comprising a ragweed pollen allergen such as Amb a1 and an immunostimulatory sequence (ISS) wherein said immunostimulatory sequence consisting of the sequence selected from the group consisting of SEQ ID NO: 1-8, and wherein the extent of conjugation in the population provides an average of ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least 1.1 in a pharmaceutically acceptable excipient for treating allergy, **does not** reasonably provide enablement for (1) *any* population of conjugate molecules, said conjugate molecule comprising *any* antigen such as *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* "polynucleotide" comprising *any* immunostimulatory sequence (ISS), wherein the extent of conjugation in the population is such that the ratio of (i) concentration of ISS-antigen conjugate required for 50%

inhibition of binding of antigen-specific antibody to antigen to (ii) concentration of antigen required for 50% inhibition of binding of antigen-specific antibody to antigen is about 3.5 to about 6.0; (2) *any* population of conjugate molecules, said conjugate molecules comprising *any* antigen such as *any* polypeptide, *any* allergen, any pollen allergen, *any* ragweed allergen and *any* polynucleotide comprising any immunostimulatory sequence (ISS), wherein the allergen is *any* allergen and wherein the extent of conjugation in the population provides a 40% histamine-release ratio of greater than about 500, said ratio calculated as the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release from basophils from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophils from an antigen-sensitized individual; (3) the population of conjugate molecules, said conjugate molecules comprising *any* antigen such as *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* polynucleotide comprising any immunostimulatory sequence (ISS), wherein the allergen is *any* allergen and wherein the extent of conjugation in the population provides a 40% histamine-release ratio of greater than about 500, said ratio calculated as the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release from basophils from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophils from an antigen-sensitized individual wherein the allergen is Amb a 1, (4) *Any* composition comprising the population of conjugate molecules, said conjugate molecule comprising *any* antigen, *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* "polynucleotide" comprising *any* immunostimulatory sequence (ISS), wherein the extent of conjugation in the population is such that the ratio of (i) concentration of ISS-antigen conjugate required for 50% inhibition of binding of antigen-specific antibody to antigen to (ii) concentration of antigen required for 50% inhibition of binding of antigen-specific antibody to antigen is about 3.5 to about 6.0 in a pharmaceutically acceptable excipient; (5) *Any* composition comprising the population of conjugate molecules, said conjugate molecules comprising any antigen and *any* polynucleotide comprising any immunostimulatory sequence (ISS), wherein the allergen is *any* allergen, *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen and wherein the extent of conjugation in the population provides a 40% histamine-release ratio of greater than about 500, said ratio calculated as the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release from basophils from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophils from an antigen-sensitized individual; (6) *any*

population of conjugate molecules, said conjugate molecules comprising *any* antigen such as *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* polynucleotide "**comprising**" an immunostimulatory sequence (ISS), wherein the extent of conjugation in the population in the population provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule; (7) *any* population of conjugate molecules, said conjugate molecules comprising any antigen such as any polypeptide, any allergen, any pollen allergen, any ragweed allergen, and *any* polynucleotide "**comprising**" an immunostimulatory sequence (ISS), wherein the extent of conjugation in the population in the population provides an average of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least 1.1; (8) The populations mentioned above wherein said immunostimulatory sequence "**comprises**" a sequence "comprises" *any* 5'-purine, purine, C,G, pyrimidine, pyrimidine, C, G-3', or *any* sequence "comprises" AACGTTCG as recited in claims 50-51, 60-61, 71-72, and 73-84 for treating *any* condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only eight specific immunostimulatory sequences (ISS) such as SEQ ID NO: 1-8 conjugated to ragweed allergen Amb a1 (See page 72). The conjugate was prepared by incubation of a mixture of ISS at various molar concentrations such as 4, 7 or 17 molar to 1 molar concentration of Amb a1. The antibody response and histamine release from various conjugates such as AIC-L (4:1), AIC-M (7:1) and AIC-H (17-1) are measured. The AIC-H (17-1) conjugate shift the Th2 to Th1 immune response as determined by IFNγ, IL-5 levels and histamine release (page 80-82). The specification discloses the term "antigen" means any substance such as peptides, proteins, glycoproteins, polysaccharides, complex carbohydrates, sugars, gangliosides lipids, and phospholipids; portions thereof and combination thereof (page 16,

liens 20-22). The specification discloses that the term "allergen" means antigen, or antigenic portion thereof of any molecule, usually a protein (see 18, lines 12-14).

The specification does not teach how to make a population of conjugate comprising *any* antigen, any allergen, any polypeptide, and any immunostimulatory sequence "**comprising**" any sequence such as the ones mentioned above, much less using any undisclosed conjugate for treating any condition. The term "antigen", "polypeptide" and "allergen" without SEQ ID NO has no structure much less function. There is insufficient guidance as to the specific amino acid sequence that makes up the structure of said antigen, polypeptide, and allergen. Further, the term "comprising" is open-ended. It expands the immunostimulatory sequence to include additional nucleotide at either end or both ends. There are insufficient guidance and working that any conjugate comprising any undisclosed antigen or polypeptide to any undisclosed nucleotide sequence would have the same structure and function as the ragweed allergen conjugated to the specific ISS for treating allergy. Given the indefinite number of antigen, polypeptide, allergen, and immunostimulatory sequence, it is unpredictable which population conjugate or composition of said population conjugate comprising the undisclosed antigen and immunostimulatory would have the same structure and function, in turn, would be useful for any purpose.

Stryer *et al* teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Van Uden *et al* (PTO 1449) teach even after intensive attempts to precisely define the DNA sequence structure required for immune stimulation, this most fundamental aspect of ISS is only partially understood (See page 903, in particular).

Given the indefinite number of antigen, polypeptide, allergen, pollen allergen, and immunostimulatory sequence, it is unpredictable which undisclosed antigen mentioned above when conjugated to any undisclosed polynucleotide sequence would have the same structure and immunostimulatory function, in turn, would be useful as a population of conjugate molecules for treating allergy. Without the amino acid sequence of any antigen, any polypeptide, any allergen and the nucleotide sequence of any immunostimulatory sequence, it would require undue

experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 78, 83-84, 86, and 90-107 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* population of conjugate molecules, said conjugate molecule comprising *any* antigen such as *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* "polynucleotide" comprising *any* immunostimulatory sequence (ISS), wherein the extent of conjugation in the population is such that the ratio of (i) concentration of ISS-antigen conjugate required for 50% inhibition of binding of antigen-specific antibody to antigen to (ii) concentration of antigen required for 50% inhibition of binding of antigen-specific antibody to antigen is about 3.5 to about 6.0; (2) *any* population of conjugate molecules, said conjugate molecules comprising *any* antigen such as *any* polypeptide, *any* allergen, any pollen allergen, *any* ragweed allergen and *any* polynucleotide comprising any immunostimulatory sequence (ISS), wherein the allergen is *any* allergen and wherein the extent of conjugation in the population provides a 40% histamine-release ratio of greater than about 500, said ratio calculated as the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release from basophils from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophils from an antigen-sensitized individual; (3) the population of conjugate molecules, said conjugate molecules comprising *any* antigen such as *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* polynucleotide comprising any immunostimulatory sequence (ISS), wherein the allergen is *any* allergen and wherein the extent of conjugation in the population provides a 40% histamine-release ratio of greater than about 500,

said ratio calculated as the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release from basophils from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophils from an antigen-sensitized individual wherein the allergen is Amb a 1, (4) *Any* composition comprising the population of conjugate molecules, said conjugate molecule comprising *any* antigen, *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* "polynucleotide" comprising *any* immunostimulatory sequence (ISS), wherein the extent of conjugation in the population is such that the ratio of (i) concentration of ISS-antigen conjugate required for 50% inhibition of binding of antigen-specific antibody to antigen to (ii) concentration of antigen required for 50% inhibition of binding of antigen-specific antibody to antigen is about 3.5 to about 6.0 in a pharmaceutically acceptable excipient; (5) *Any* composition comprising the population of conjugate molecules, said conjugate molecules comprising any antigen and *any* polynucleotide comprising any immunostimulatory sequence (ISS), wherein the allergen is *any* allergen, *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen and wherein the extent of conjugation in the population provides a 40% histamine-release ratio of greater than about 500, said ratio calculated as the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release from basophils from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophils from an antigen-sensitized individual; (6) *any* population of conjugate molecules, said conjugate molecules comprising *any* antigen such as *any* polypeptide, *any* allergen, *any* pollen allergen, *any* ragweed allergen, and *any* polynucleotide "**comprising**" an immunostimulatory sequence (ISS), wherein the extent of conjugation in the population in the population provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule; (7) *any* population of conjugate molecules, said conjugate molecules comprising any antigen such as any polypeptide, any allergen, any pollen allergen, any ragweed allergen, and *any* polynucleotide "**comprising**" an immunostimulatory sequence (ISS), wherein the extent of conjugation in the population in the population provides an average of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least 1.1; (8) The populations mentioned above wherein said immunostimulatory sequence "**comprises**" a sequence "comprises" *any* 5'-purine, purine, C,G, pyrimidine, pyrimidine, C, G-3', or *any* sequence "comprises" AACGTTCG as recited in claims 50-51, 60-61, 71-72, and 73-84 for treating *any* condition.

The specification discloses only eight specific immunostimulatory sequences (ISS) such as SEQ ID NO: 1-8 conjugated to ragweed allergen Amb a1 (See page 72). The conjugate was prepared by incubation of a mixture of ISS at various molar concentrations such as 4, 7 or 17 molar to 1 molar concentration of Amb a1. The antibody response and histamine release from various conjugates such as AIC-L (4:1), AIC-M (7:1) and AIC-H (17-1) are measured. The AIC-H (17-1) conjugate shift the Th2 to Th1 immune response as determined by IFNγ, IL-5 levels and histamine release (page 80-82). The specification discloses the term "antigen" means any substance such as peptides, proteins, glycoproteins, polysaccharides, complex carbohydrates, sugars, gangliosides lipids, and phospholipids; portions thereof and combination thereof (page 16, liens 20-22). The specification discloses that the term "allergen" means antigen, or antigenic portion thereof of any molecule, usually a protein (see 18, lines 12-14).

With the exception of the specific population of conjugate comprising the specific immunostimulatory sequence (ISS) and the specific allergen, there is insufficient written description about the structure associated with function of any population of conjugate molecules or composition mentioned above because the term "antigen", "allergen", "pollen allergen" and "polypeptide" without SEQ ID NO: have no structure, let alone having the same functions as ragweed allergen Amb a1. As to immunostimulatory sequence (ISS), the term "comprises" is open-ended. It expands the immunostimulatory sequence, which is a nucleotide sequence, to include additional nucleotide to either or both ends. There is inadequate written description about the additional undisclosed nucleotide added to the ISS, much less about having the same immunostimulatory functions as the specific ISS.

Further, the specification discloses only one pollen allergen Amb 1 conjugated to one ISS (SEQ ID NO: 1). Given the lack of a written description of *any* additional representative species of allergen, polypeptide, antigen, pollen allergen and ISS as encompassed by the claims for a population of conjugate, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 50-51, 60-61, 71-72, and 83-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "G-3'"" in claims 50 has no antecedent basis in base claim 45 because the word "G", which is a purine at the 3'end is not recited in claim 45. Claim 45 requires a pyrimidine at the 3' end. Claim 45 should depends on claim 1.

The recitation of "G-3'"" in claims 60 has no antecedent basis in base claim 56 because the word "G", which is a purine at the 3'end is not recited in claim 56. Claim 56 requires a pyrimidine at the 3' end. Claim 45 should depends on claim 2.

The recitation of "G-3'"" in claims 71 has no antecedent basis in base claim 66 because the word "G", which is a purine at the 3'end is not recited in claim 66. Claim 66 requires a pyrimidine at the 3' end. Claim 71 should depends on claim 63.

The recitation of "G-3'"" in claims 83 has no antecedent basis in base claim 78 because the word "G", which is a purine at the 3'end is not recited in claim 78. Claim 78 requires a pyrimidine at the 3' end. Claim 83 should depends on claim 75.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-3, 50-51, 60-61, 71-72, 75, 83-84, 86, and 90-107 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/16247 publication (April 1998, PTO 1449).

The WO 98/16247 publication teaches a composition of conjugate molecule wherein the conjugate molecule comprises an antigen (IMM) such as β-gal (polypeptide) or a pollen allergen polypeptide such as Amb a I (page 19, lines 15-22, in particular) conjugated to a polynucleotide comprising an immunostimulatory sequence (ISS-PN or ISS-ODN) such as 5'TGACTGTGAACGTTCGAGATGA-3' (DY1018) (See page36, line 10, in particular) and a pharmaceutically acceptable excipient for modulating an immune response (See claims of the

WO 98/16247, page 24, lines 9-27 bridging page 25, lines 1-9, in particular). The term "comprising" is open-ended. It expands the claimed ISS to include the reference ISS. The reference immunostimulatory sequence 5' **AACGTTCG 3'** where nucleotides A and G are purine and nucleotide C and G are pyrimidine. The WO 98/16247 publication teaches the linking of the reference IMM to the reference ISS can be made in a variety of way such through a linker N-Hydroxysuccinimide ester that reacted directly with the N4 amino group of cytosine residues and depending on the number and location of cytosine residue in the ISS, specific labeling (linking) at one or more residues can be achieved (See page 24, lines 1-4, I particular) and various linkage known in the art (See pages 24-26, in particular). The WO 98/16247 publication further teaches that the concentration of the conjugate to the antigen is 5: 1, which is at least 1.1 (See page 7, in particular). With regard to 50% inhibition of binding of antigen-specific antibody to antigen, it is an inherent property of the reference-conjugated antigen since the process of conjugation alters the structure of said antigen. The WO 98/16247 publication further teaches that the reference conjugate molecule such as ISS-PN, ISS-PN/IMM can shift the host cellular immune response away from the helper T lymphocyte type 2 (Th2) phenotype toward a helper T lymphocyte type 1 (Th1) phenotype and using this method to boost the immune responsiveness of a host to subsequence challenge by a sensitizing antigen without immunization can avoid the risk of Th2-mediated, immunization-induced anaphylaxis by suppressing IgE production in response to the antigen challenge. Furthermore, the conjugate molecule is especially advantageous for treatment of localized allergic response (See page 3, lines 8-23, in particular). The WO 98/16247 publication teaches allergen such as Amb a1 of ragweed pollen allergen can be conjugate to the polynucleotide comprising the immunostimulatory sequence (ISS-PN or ISS-ODN) (See page 19, lines 15-22, page 21-26, in particular). The reference population of conjugate inherently reduces histamine release and block binding. Claims 63 and 75 are included in this rejection because the extent of conjugation is the inherent method steps that depend on the reaction time. The shorter the reaction time, the concentration of antigen-ISS-ODN conjugate would be less and smaller (less mass). Conversely, the longer the reaction time, the more antigen-ISS-ODN would form and the larger the aggregate (more mass) until equilibrium is reached. The recitation of "**an average** of at least 5.5 ISS containing polynucleotides per antigen molecule (5.5:1 ration)" in claim 63 would include the reference conjugate at 5:1 (ISS:antigen) ratio, since some of claimed conjugate in the population is 5:1 ratio, some are at 6:1 ratio and others are at 4:1 ratio. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 9/30/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the figure legends of Carson et al state that the ISS/antigen conjugate employed are at a 5:1 (ISS:antigen) ratio. In contrast, claims 1 and 2 recite a population of conjugates which are conjugated to an extent that results in: a 50% binding inhibition ratio of about 3.5 to about 6.0 and a 40% histamine release ratio of greater than about 500. (2) Carson et al fail to teach anything with respect to any desirability or effect of the extents of conjugation and contain no disclosure regarding variation of the ratio or reaction time. (3) New claims 63 and 75 recite a population of conjugate polynucleotide to antigen of at about 5.5 (claim 63) and an average of mass ratio of ISS-containing polynucleotide to antigen of at least 45 to 40, or an average mass ratio of at least 1.1 (claim 75).

However, the WO 98/16247 publication teaches a composition of conjugate molecule wherein the conjugate molecule comprises an antigen (IMM) such as β-gal (polypeptide) or a pollen allergen polypeptide such as Amb a I (page 19, lines 15-22, in particular) conjugated to a polynucleotide comprising an immunostimulatory sequence (ISS-PN or ISS-ODN) such as 5'TGACTGTGAACGTTCGAGATGA-3' (DY1018) (See page36, line 10, in particular) and a pharmaceutically acceptable excipient for modulating an immune response (See claims of the WO 98/16247, page 24, lines 9-27 bridging page 25, lines 1-9, in particular). The term "comprising" is open-ended. It expands the claimed ISS to include the reference ISS. The reference immunostimulatory sequence 5' **AACGTTCG 3'** where nucleotides A and G are purine and nucleotide C and G are pyrimidine. The WO 98/16247 publication teaches the linking of the reference IMM to the reference ISS can be made in a variety of way such through a linker N-Hydroxysuccinimide ester that reacted directly with the N4 amino group of cytosine residues and depending on the number and location of cytosine residue in the ISS, specific labeling (linking) at one or more residues can be achieved (See page 24, lines 1-4, I particular) and various linkage known in the art (See pages 24-26, in particular). The WO 98/16247 publication further teaches that the concentration of the conjugate to the antigen is 5: 1, which is at least 1.1 (See page 7, in particular). The inhibition of binding due to higher titer of IgG 2a, (See Fig 3, IgE-ISS of the WO98/1627) and lower antigen specific IgE, in turn, lower histamine release due to anti-IgE crosslinks the Fc receptors on mass cell or basophils are the inherent properties of the reference conjugate containing the immunostimulatory sequence since the reference ISS-PN/IMM stimulates a strong Th1 type cellular immune response such as IFNγ. The recitation of

"**an average** of at least 5.5 ISS containing polynucleotides per antigen molecule (5.5:1 ration)" in claim 63 would include the reference conjugate at 5:1 (ISS:antigen) ratio, since some of claimed conjugate in the population is 5:1 ratio, some are at 6:1 ratio and others are at 4:1 ratio.

In response to applicant's argument that Carson et al fails to teach anything with respect to any desirability or effect of the extents of conjugation and contains no disclosure regarding variation of the ratio or reaction time, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Patent Examiner
Technology Center 1600
December 16, 2002

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TECHNOLOGY CENTER 1600